Public and Private Sector Contributions to the Discovery and Development of 'Impact' Drugs

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Executive Summary

Recently, well-publicized reports by Public Citizen and the Joint Economic Committee (JEC) of the U.S. Congress questioned the role of the drug industry in the discovery and development of therapeutically important drugs. To gain a better understanding of the relative roles of the public and private sectors in pharmaceutical innovation, the Tufts Center for the Study of Drug Development (Tufts CSDD) evaluated the underlying National Institutes of Health (NIH) and academic research cited in the Public Citizen and JEC reports, and performed its own assessment of the relationship of the private and public sectors in drug discovery and development of 21 'impact' drugs. The following are the major findings of this analysis:

- In August 2001, NIH released *A Plan to Ensure Taxpayer's Interests Are Protected* in response to Congress's concern that NIH is securing appropriate return on its investment in basic research for therapeutic drugs with more than $500 million per year in U.S. sales. NIH identified 47 drugs that fit the sales threshold criteria, but only 4 drugs for which the government could claim "use or ownership rights." This result conflicts with the findings of the Public Citizen and JEC reports because different methods were used to assess NIH "ownership" of the drugs.

- In February 2000, the NIH completed the administrative document *NIH Contributions to Pharmaceutical Development — Case Study Analysis of the Top-Selling Drugs* to determine the extent to which publicly funded research contributed to the development of certain medically or commercially successful products. Their methodology consisted of reviewing the scientific literature for the names and affiliations of scientists responsible for basic research that led to drug discovery. This methodology overestimated the public sector contribution because of its focus on basic research, and underestimated the private sector contribution because industry scientists have less incentive to publish. Also, information on funding and co-authorship by academia and industry were incomplete.

- Economists Iain Cockburn and Rebecca Henderson have written several papers evaluating the relative contributions of the private and public sectors to the discovery and development of 21 drugs "having had the most impact" on therapeutics from 1965 to 1992. In their analysis, the authors determined which sector was responsible for the key enabling discovery and first synthesis of the drug. While the Public Citizen and JEC reports both note that approximately 75% of the key enabling discoveries were made in the public sector, they do not acknowledge that 78% of these drugs were first synthesized by pharmaceutical industry scientists.

- Tufts CSDD's investigation of the 21 'impact' drugs found that using simple publication counts is not a reliable method to quantify the relative contributions of the public and private sector for the following reasons: industry contributions tend to be underestimated; the relevance of NIH-funded clinical studies cannot be determined; and, the substantial amount of non-U.S. research and development undertaken on these drugs complicates the valuation of the roles of the U.S. public and private sectors.

Ultimately, any attempt to measure the relative contribution of the public and private sectors to the R&D of therapeutically important drugs by output alone, such as counting publications or even product approvals, is flawed. NIH is

not in the business of marketing drugs, any more than pharmaceutical industry scientists are employed solely to author journal publications. By the same token, it is equally flawed to measure relative contributions to the R&D of innovative drugs solely by the source and size of the monetary investment. Several key factors — e.g., the degree of uncertainty, the expected market value, and the potential social benefit — affect investment decisions, and determine whether public or private sector funds, or both, are most appropriate. Because of the competitiveness and complexity of today's R&D environment, both sectors are increasingly challenged to show returns on their investment, and the traditional boundaries separating the roles of the private and public research spheres have become increasingly blurred. What remains clear, however, is that the process still starts with good science and ends with good medicine.

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Introduction

A recent, widely publicized report has disparaged the contribution of the drug industry to the development of important new drugs. In July 2001, Public Citizen, a consumer watchdog group, released a report called *Rx R&D Myths: The Case Against the Drug Industry's R&D "Scare Card,"* which stated that, "Industry R&D risks and costs are significantly reduced by taxpayer-funded research, which has helped launch the most medically important drugs in recent years…."[1] Industry critics have also used a report entitled *The Benefits of Medical Research and the Role of the NIH*, which was issued in May 2000 by the Joint Economic Committee (JEC) of the U.S. Congress, to minimize the role of industry in the discovery and development of innovative drugs. The JEC report focused on a group of 21 drugs introduced from 1965 to 1992 "…that were considered by experts to have had the highest therapeutic impact on society…."[2] Public Citizen and the JEC cited research done by the National Institutes of Health (NIH), as well as a study done by economists Iain Cockburn and Rebecca Henderson, in support of their claims.

A count of published studies of specific drugs cannot be used to assign values to relative public and private contributions to their development.

The findings of the Public Citizen report regarding the relative contribution of the public and private sector to drug discovery and development were based on one document in particular — an internal NIH study entitled *NIH Contributions to Pharmaceutical Development — Case Study Analysis of the Top-Selling Drugs*. This document, which was made widely available by Public Citizen in July 2001, purported to demonstrate the respective roles of the public and private sectors in the development of five top-selling drugs through analyses of published literature. However, a fundamental defect underlying studies of this kind is the subjective nature of assigning relevance. A count of published studies of specific drugs cannot be used to assign values to relative public and private contributions to their development because the relevance of the studies to the ultimate approval of the drugs often cannot be determined.

The impact of publicly funded biomedical research on private sector drug discovery and development efforts was also investigated by Cockburn and Henderson. The focus of Cockburn and Henderson's work was the relationship between private sector firms' participation in "open science," as measured by counting coauthorship of scientific papers with public sector scientists, and the productivity of their in-house research.[3] Cockburn and Henderson used case histories of 21 drugs to illustrate their point, but they did not attempt quantitative analyses of the relative contributions of the public and private sectors to the discovery and development of these drugs. In fact, Cockburn and Henderson acknowledged in their paper that it was difficult to quantify the public sector's specific contribution to the industry's pool of knowledge capital. The authors surmised that this difficulty was due to the long lags between fundamental discoveries and consequent marketed products, and the "…complex and often bidirectional relationship between the public and private sectors…."[4] The authors emphasized that their analysis was an attempt to measure the extent and nature of the "connectedness" between the public and private sectors. Specifically, they examined the ability of industry to access the common pool of useful knowledge generated by public sector research, thereby enhancing industry's productivity.[5] Despite methodological limitations noted by the authors, Cockburn and Henderson's work has

been used to paint an unflattering picture of the contribution of industry to the research and development of many breakthrough drugs.

A clear counterpoint to the JEC and Public Citizen reports emerged from the most recent report by NIH on this contentious and complex subject. In August 2001, the NIH released *A Plan to Ensure Taxpayers' Interests Are Protected*.[6] The plan was devised in response to the Committee Report for FY 2001 Department of Health and Human Services (DHHS) Appropriation, in which the NIH was instructed to prepare a plan to ensure taxpayers' interests are protected when NIH invests in basic research. Specifically, NIH was directed to review a list of FDA-approved therapeutic medicines that had $500 million/year sales in the United States, and had received NIH funding, when preparing the plan.

. . . assessment of government patent rights as a measure of NIH "ownership" of a drug brings a new perspective to the question of whether the public is getting an appropriate return on the NIH investment in basic research.

According to NIH, only four of 47 drugs meeting the criteria were developed with patented technologies for which the government has use or ownership rights. This finding was derived from a review methodology that focused on practical considerations of the NIH's mission, and on legal aspects of the Stevenson-Wydler Technology Innovation Act and the Patent and Trademark Amendments of 1980 (known as the Bayh-Dole Act), as implemented by NIH. The picture of the relative contribution of the public and private sector to drug development when this methodology is employed bears sharp contrast to the image portrayed in the JEC and Public Citizen reports.

In this white paper, we first review the pertinent points of the recent analysis conducted to formulate the NIH plan to protect taxpayers' interests regarding NIH-funded research. We demonstrate that assessment of government patent rights as a measure of NIH "ownership" of a drug brings a new perspective to the question of whether the public is getting an appropriate return on the NIH investment in basic research. We next examine the studies by NIH (as cited in the Public Citizen report) and Cockburn and Henderson, which used publications as a measure of public and private contributions to the discovery and development of specific best-selling, 'impact' drugs. These studies in particular have been used to imply that NIH has "ownership," at least in part, of the drugs. We explore the methodology used in these studies, and discuss their limitations. Finally, we provide an independent assessment of the very complex and interdependent relationship of the public and private sectors in drug discovery and development.

NIH response to the Committee Report for the FY 2001 DHHS Appropriation instruction:

A Plan to Ensure Taxpayers' Interests Are Protected (released August 2001)

The following instructions were given to NIH in the Committee Report for the FY 2001 DHHS Appropriation:

"The conferees have been made aware of the public interest in securing an appropriate return on the NIH investment in basic research. The conferees are also aware of the mounting concern over the cost to patients of therapeutic drugs. By July 2001, based on a list of such therapeutic drugs which are FDA

approved, have reached $500 million per year in sales in the United States, and have received NIH funding, NIH will prepare a plan to ensure that taxpayers' interests are protected."[7]

In responding to the instructions, NIH noted the legal framework into which it is bound, described the process NIH uses to fund research, discussed the methodology and findings, then proposed a plan. The overall conclusion was that, "NIH and its recipient institutions apply the provisions of Bayh-Dole to best advantage in seeking the optimal return on investment in terms of public health benefit."[8] After noting the difficulty in associating particular NIH grants and contracts that gave rise to inventions with patents or licenses for the final product, NIH proposed a plan to initiate better information collection, and development of a web-based database that would allow NIH to make the required associations.

The key phrase of the conclusion was "apply the provisions of Bayh-Dole." The NIH has strict limitations under Bayh-Dole — NIH does not have title to grants-supported or contracts-supported (extramural) research discoveries, and cannot dictate terms for licensing or commercialization of the work. Support for this extramural research, which is done by non-Federal researchers at academic, medical, and research institutions in the U.S. and abroad, accounts for nearly 84% of the NIH budget.[9]

As per the instructions, NIH identified 47 drugs that fit the designated criteria, and then determined whether the government, either directly or through a grantee or contractor, held patent rights, or was designated as having an interest on the patents of the 47 drugs. NIH found that, "NIH has Government use or ownership rights to patented technologies used in the development of four of those drugs."[10]

NIH case study report:

NIH Contributions to Pharmaceutical Development — Case Study Analysis of the Top-Selling Drugs (Administrative document prepared by NIH staff, February 2000)[i]

The NIH case study report was undertaken to determine whether and to what extent public funding of research enabled the development of certain medically or commercially successful products. Additionally, this study began to lay a basis for discussing the specific ways by which those who expand fundamental understanding of the workings of the natural world are as important to technological advance as those who implement that knowledge.[11]

The NIH case study report was prepared from an analysis of review articles identified by Medline searches of the chemical name of the drugs and original research articles cited by the reviews. The literature selected for inclusion in the report was focused on basic research, as stated in the methodology section: "The scientific discoveries that led to the necessary concepts and techniques were identified, along with the names and affiliations of the scientists performing the work. Rather than attempt to identify a small number of "key papers," which does not accurately represent the way scientific ideas develop in the research community, *the approach taken was to identify major areas of research which led to drug discovery* and the individuals or laboratories who were significantly involved." [emphasis added] Despite the focus on basic research, the report included sections listing publications in the areas of "drug development and testing" and "clinical trials."

[i] Public Citizen acquired the NIH case study report through a Freedom of Information Act request and posted the report on their website on July 23, 2001. The NIH case study report is cited in the JEC report released in May 2000.

We examined the NIH case study report and found the study to be limited in the following ways:

- The methodology is inherently biased toward public sector input. Specifically, public sector scientists have a much greater incentive to publish than do industry scientists.
- Industry contribution is underestimated because a number of publications co-authored by academic and industry scientists are assigned only to public sector affiliation. A category for the co-authored publications, the main focus of Cockburn and Henderson's work, does not exist in the NIH case study report.
- The list of published studies included in the sections on "drug development and testing" and "clinical trials" is not complete. Therefore these sections cannot be used for quantitative analyses.
- Industry contribution could be underestimated, since complete information on the funding of the published studies is not provided. Thus, though the scientist's affiliation was academic, funding for the work might have been wholly, or in part, from industry.
- No information is given as to whether the NIH grants were for extramural or intramural research. The distinction has implications due to the legal limitations on NIH "ownership" of technology resulting from extramural work.

Cockburn and Henderson papers:

Public-Private Interaction and the Productivity of Pharmaceutical Research (4/97 working paper)

Absorptive Capacity, Coauthoring Behavior, and the Organization of Research in Drug Discovery (6/98)

Iain Cockburn and Rebecca Henderson have written a number of papers on the topic of public-private interaction in pharmaceutical research. Their work has been cited by NIH, the JEC, and by Public Citizen. As part of their work, Cockburn and Henderson constructed case histories for a group of 21 drugs that were considered to have had the most impact upon therapeutic practice between 1965 and 1992. They then attempted to answer two questions concerning the drugs. These two questions were:

1. Was the key enabling discovery made by a scientist working in the public sector? (Yes/No)

2. Was the drug first synthesized or isolated by a scientist working in the public sector? (Yes/No)

Answers to the first question led Cockburn and Henderson to state that "only 5 of these drugs, or 24%, were developed with essentially no input from the public sector."[12,13]

This particular statement has been cited in various ways. The JEC cites the Cockburn and Henderson working paper and states, "71 percent (15 drugs) were developed with input from the public sector."[14] Public Citizen cites the same paper and states, "A study by a Massachusetts Institute of Technology (MIT) scholar of the 21 most important drugs introduced between 1965 and 1992 found that

publicly funded research played a part in discovering and developing 14 of the 21 drugs (67 percent)."[15] The NIH case study report cites an unpublished version of the work prepared for a conference in June 1996 and declares, "among these 21 drugs, publicly-funded research was instrumental to the development of 16, or 76%."[16]

These statements by JEC, Public Citizen, and NIH are alike in one important way — none of them mention the fact that the "publicly-funded research" was for key enabling discoveries only. Cockburn and Henderson provide this information for 19 of the 21 drugs in the working paper (key enabling discoveries for 14 are assigned to public sector scientists). Interestingly, JEC, Public Citizen, and NIH make no reference to the answers to their second question. Cockburn and Henderson's second result was that 14 (78%) of the drugs were first synthesized by industrial scientists (information provided for 18 of the 21 drugs).

Both the NIH and the pharmaceutical industry are vulnerable to criticism.

Use and misuse of the NIH case study report, and Cockburn and Henderson's work

The NIH case study report and Cockburn and Henderson's work are in agreement in their finding that publicly funded research efforts in medicine and the pharmaceutical industry's research and development efforts are, on the whole, complementary. Publicly funded research tends to focus on basic science, while the pharmaceutical industry tends to focus on applied research and clinical studies of promising drugs, though there is some overlap of these areas.

The NIH should be recognized for its long history of achievements and contributions to medicine, and for its five Nobel laureate scientists. In addition, NIH has funded excellent science over the years, as evidenced by the 93 Nobel Prizes won by NIH-funded scientists.[17] The pharmaceutical industry should also be recognized for its excellent research and development efforts, which have resulted in the approval for marketing of 438 new medicines in the U.S. during the last 20 years,[18] and of the three scientists who won Nobel Prizes while working in the private sector.

Both NIH and the research-based pharmaceutical industry have sponsored studies designed to illustrate the importance of their work. Issues arise when "facts," some of which are incorrect or used out of context, from these studies are used in an attempt to demonstrate the greater value of one group's efforts compared to the other. Both the NIH and the pharmaceutical industry are vulnerable to criticism. NIH is sensitive to criticism that a proportion of its funding goes to projects that do not produce tangible results. The pharmaceutical industry is equally sensitive to criticism that all the hard work of drug discovery is done by publicly funded researchers, and that industry unfairly profits by simply marketing the resulting drugs.

Counting publications that involve use of the drug is a biased way of assigning "ownership" of the drug. NIH's "ownership" of medical research cannot be determined by counting the number of new medicines it markets because NIH is not in the business of marketing drugs. By the same token, the pharmaceutical industry's "ownership" of marketed drugs cannot be determined by counting publications because industrial scientists typically are employed to produce commercial products, not publications.

Tufts CSDD investigation: Public and private sector contributions to the discovery and development of 'impact' drugs

We independently studied the case histories of the 21 'impact' drugs included in the Cockburn and Henderson work. Using an approach similar to that described in the NIH case study report, we searched the published literature for information on the discovery and development of the drugs. We noted the affiliation and location of the authors, the source of funding for the work (if provided by authors), and the date of the study (if provided) or publication. We restricted our search to papers that pertained to a given drug and were published between the year of the synthesis of the drug and two years after U.S. approval of the drug.[ii] We did not duplicate the study of the enabling discoveries done both by NIH and by Cockburn and Henderson, but focused only on published studies that reported properties (e.g., chemical, physical, toxicologic, pharmacokinetic/dynamic, therapeutic) of the actual drugs. The 21 drugs we studied are listed in Table I.

The following points should be noted:

- The limitations inherent in our methodology were the same as for the NIH case study report — industry contributions tended to be underestimated because contributions were assigned to published work only.
- Our results, like those in the NIH case study report, cannot be used for quantitative analyses — we identified hundreds of publications that met our criteria; some of the publications were hundreds of pages in length (these were proceedings of symposia). It was not possible to ascertain whether we found all pertinent publications (e.g., only publications in English were included).
- There was substantial non-U.S. involvement in the discovery and development work done for the 21 drugs — the majority of the drugs were synthesized, patented, or first launched outside of the U.S., which complicated any analyses of the relative contributions of the public and private sectors.
- The relevance of any clinical studies funded wholly or in part by the NIH to the approval of the drug could not be determined.

Our study illustrates the complex interactions of the U.S. public sector, especially the NIH, and the private sector in the discovery and development of drugs. For this set of 21 drugs, we noted that the involvement of NIH, usually in the form of extramural research funding, was greatest in the preclinical and clinical development of drugs that were treatments for serious or life-threatening diseases, such as AIDS or cancer. There was clearly a public health benefit derived from facilitating the development of these drugs. NIH was also involved in the discovery and/or development of compounds that were in the "public domain," i.e., knowledge of the existence and method of preparation of the

[ii] Additional clinical testing funded by the U.S. public sector may have occurred after the drugs were approved for marketing. It is important to note that after approval, drugs may be tested in clinical studies by any qualified investigator. Since the drug is commercially available, the FDA does not necessarily have to be informed of the clinical studies (although IRB and informed consent regulations still apply), and involvement or consent of the manufacturer is not required.

Table I

Name of sponsoring company	Generic name	Trade name	Year of synthesis (bio. activity)	Location of company head-quarters	Non-US synthesis	Non-US patent priority	First marketed outside US	Year of first launch	Year of US launch
Burroughs Wellcome	acyclovir	Zovirax	1974	UK (US facility)	N	Y	Y	1981	1982
Burroughs Wellcome	AZT	Retrovir	1963 (1980)	UK (US facility)	N	Y	N	1987	1987
Squibb	captopril	Capoten	1974	US	N	N	N	1981	1981
Smith Kline French	cimetidine	Tagamet	1972	US (UK facility)	Y	Y	Y	1976	1977
Bristol-Myers	cisplatin	Platinol	1845 (1965)	US	Y	Y	N	1979	1979
Sandoz	cyclosporin	Sandimmune	1970 (1972)	Switzerland	Y	Y	N	1983	1983
Amgen	erythropoietin	Epogen	1985 (1970)	US	N	N	Y	1988	1989
Merck	finasteride	Proscar	1983	US	N	N	N	1992	1992
Pfizer	fluconazole	Diflucan	1981	US (UK facility)	Y	Y	Y	1988	1990
Eli Lilly	fluoxetine	Prozac	1970	US	N	N	Y	1986	1988
Astra	foscarnet	Foscavir	1924 (1978)	Sweden	Y	Y	Y	1989	1991
Pfizer	gemfibrozil	Lopid	1968	US (UK facility)	N	N	N	1982	1982
Berlex/Chiron	interferon ß-1b	Betaseron	1980	Germany/US	N	N	N	1993	1993
Janssen	ketoconazole	Nizoral	1976	Belgium	Y	N	N	1981	1981
Merck	lovastatin	Mevacor	1979	US	N	N	N	1987	1987
Bayer	nifedipine	Procardia	1967	Germany	Y	Y	Y	1975	1982
Astra	omeprazole	Prilosec	1979	Sweden	Y	Y	Y	1988	1989
Glaxo	ondansetron	Zofran	1983	UK	Y	Y	Y	1990	1991
ICI (Zeneca)	propranolol	Inderol	1964	UK	Y	Y	N	1967	1967
Glaxo	sumatriptan	Imitrex	1984	UK	Y	Y	Y	1991	1993
ICI (Zeneca)	tamoxifen	Nolvadex	1962	UK	Y	Y	Y	1973	1978

Note: Date of discovery of biological activity is listed separately if different from date of synthesis.

compounds was publicly available before therapeutic potential was identified. Three of the drugs (AZT, cisplatin, foscarnet) were synthesized well before biological activity was observed. These types of compounds initially might not have been of interest to the pharmaceutical industry because possible patent claims were limited.

Having acknowledged the contribution of the public sector, in particular the NIH, in the development of the impact drugs just discussed, it is important to note that NIH cannot patent or in any other way claim "ownership" of drugs simply by funding studies. It is also necessary to place the part played by NIH funded trials in the overall picture of drug development. No one would argue that during the period in which many of the 21 drugs from our review were in active development, public funding in real terms in the U.S. for health-related research increased by 200%.[19] However, the majority of that health-related research was not focused on pharmaceuticals. NIH's definition of "clinical research" has been criticized as being too inclusive, since it encompasses not only clinical trials but also mechanisms of human disease, therapeutic interventions, development of new technologies, epidemiologic and behavioral studies, as well as outcomes and health services research.[20]

According to a recent study by the General Accounting Office (GAO), even NIH's use of the term "clinical trials" includes a range of research activities encompassing testing of new approaches to disease prevention, diagnosis, or treatment.[21] The GAO report further acknowledges that while both NIH and pharmaceutical companies are the major sponsors of clinical trials that focus on drugs, devices and vaccines, the NIH-supported trials also address prevention strategies and surgical procedures, and may target special populations, such as patients with rare diseases.[22] The pharmaceutical industry, in contrast, typically supports the large clinical trials that determine therapeutic efficacy of new drug products for conditions that affect large numbers of people.[23]

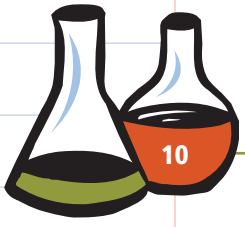
Drug development is a resource-intensive undertaking that requires commitment of time, capital, and manpower.

"Nobel Prize winning" drug research: the product of time, capital, and manpower

The importance of the contribution of the private sector to drug discovery and development was acknowledged when the 1988 Nobel Prize in Physiology or Medicine was awarded to Dr. George Hitchings, Ms. Gertrude Elion, and Sir James Black for their discoveries of important principles for drug treatment. Hitchings and Elion, working at Burroughs Wellcome, contributed to the discovery and development of acyclovir.[iii] Black contributed to the discovery and development of propranolol and cimetidine, while working at Imperial Chemical Industries and later SmithKline & French.[iv]

[iii] Hitchings joined Burroughs Wellcome in 1942, and became Vice President in charge of research in 1967. Elion joined Burroughs Wellcome in 1944 and was Head of the Department of Experimental Therapy from 1967 to 1983.

[iv] Black was a research scientist at Imperial Chemical Industries (ICI), where he worked from 1958 to 1964 on the ß-receptor antagonist program that resulted in the discovery and development of propranolol. He then moved to SmithKline & French where he worked from 1964 to 1972 on the H2-receptor antagonist program that resulted in the discovery and development of cimetidine.



The history of the discovery and development of the drugs that garnered their inventors the coveted Nobel Prize illustrates another point — drug development is a resource-intensive undertaking that requires commitment of time, capital, and manpower. For example, Burroughs Wellcome's antiviral discovery program was active for six years before acyclovir was synthesized in 1974 at the U.S. facility. In the decade that followed, further R&D involving biological activity screens (plaque reduction and inhibition) and preclinical work (mouse, guinea pig, rabbit models) was done at the facility in England, ultimately requiring 330 'scientist years' and millions of pounds sterling.[24]

Similarly, Imperial Chemical Industries' ß-receptor antagonist program was active for six years before propranolol was synthesized in 1964. Sir James Black noted that his co-workers' use of deductive organic chemistry, understanding of the link between drug delivery and effect, and development of analytical methods for estimating the levels and tissue distribution of a drug and its metabolites were crucial to the discovery and development of propranolol.[25]

Finally, SmithKline & French's histamine H2-receptor antagonist program was initiated in 1964. By mid-1970, over 700 compounds had been synthesized and tested for bioactivity; several (burimamide and metiamide) were tested in humans. Approximately 150 scientists were involved in the program. Cimetidine was synthesized in 1972, tested in normal volunteers in March 1975, first given to patients in November 1975, and marketed in England in November of 1976. The rapid pace of the development program was a result of the knowledge gained from the work that had been done on the precursor compounds.

These examples illustrate the point that drug discovery is a time-consuming process requiring the synthesis and in-vitro screening of many compounds before one with the best properties is selected for clinical testing. *A priori*, there is no guarantee that a drug discovery program will be successful. Moreover, even after a promising candidate is discovered, there are many more steps to the process (e.g., formulation, stability testing, preclinical testing) before the drug can be studied in the clinic (see Table II).

Success Has Many Fathers

The composite history of the 21 impact drugs reveals that the public and private research spheres are symbiotic, sustaining each other in both expected and unexpected ways. The public sector is often responsible for basic science research that lays the groundwork for new drugs (e.g., such as modern genetics did for interferon beta-1b), or even research into new uses for old drugs. Still other public sector research contributes to the clinical knowledge used in the design of efficacy tests for discovered drugs (e.g., finasteride), or epidemiological and long-term health outcome studies (e.g., the intervention studies of gemfibrozil by the U.S. Dept. of Veterans Affairs) needed to establish new directions for drug related studies, so-called agenda-setting research.[26]

But even those functions are interchangeable, as private sector development of new therapeutic agents often benefits basic research in the public sector by enabling scientists to explore the way the body works at the cellular level, such as occurred with cyclosporin and

Table II

Time	Steps in Discovery, Development and Regulatory Approval	Production Processes, Equipment, Materials, and Personnel	Costs, Risks, Delays and Failures
Decades	**Basic Research:** Research on fundamental mechanism of disease, biological process, and action of known therapeutic agents ▶ Drug concept.	NIH extramural grants support research in over 2,000 universities, medical schools, hospitals, small businesses, and research institutions in the U.S. and abroad.	Can take decades to produce a drug concept. Average NIH research grant for new clinical trials was $600,000 in 1996.
Three to Five Years	**Discovery:** Random selection, broad biological screening, structure/activity relationship (SAR) analysis, bioinformatics, serendipity ▶ Lead compound (investigational drug/biologic).	Combinatorial chemistry using robots to synthesize thousands of molecules. High through-put screening for toxicity and biological activity using robotics and miniaturized formats. In vitro testing with human liver microsomes	At one large pharma company in 1997, even with the capacity to construct 2 million compounds and screen 35 million compounds per year, only 18 entered exploratory development.
	Synthesis & Early Testing: Chemical synthesis of small molecules. Extraction from natural sources by fermentation and biotechnology. Early pharmacology studies to explore the pharmacological activity and therapeutic potential of compounds begins ▶ Active Pharmaceutical Ingredient (API).	Tests involve the use of animal tissues, isolated cell cultures, isolated enzymes, cloned receptor sites and computer models. Assay lead compound for strength, potency or impurities. Separate API from impurities, degradation products and inert excipients. From starting material, API needed only in gram quantities.	There are multiple sequential chemical or biological reactions yielding desired intermediates; entire synthesis pathway must be charted and validated. Time frame for completion of multiple sequential steps increases from 1 week to 1 month for each reaction step.
	Preclinical, Formulation and Stability Tests: preclinical animal pharmacology and toxicology to determine potential risks of API to man and the environment. Manufacturer must demonstrate company's capacity to produce a product in large volume and ensure chemical stability, batch-to-batch uniformity, and overall product quality.	Involves use of animals, tissue culture, and other test systems to examine relationship of dose, frequency of administration, and duration of exposure to short and long-term survival; requires veterinarians, toxicologists, as well as animal and lab technicians.	Costs of animal studies rose 3-6 fold from 1980-1990, testing in 2000 would range from $20 thousand for acute rat toxicity study to $2 million for 2-yr. rat bioassay. Drug has to show an adequate safety profile in animal toxicology testing.
		Ramp-up production of API to kilogram levels; each of multiple steps in synthesis needs to be systematically investigated and scaled-up. Early batches must be characterized for purity, impurity, physical and chemical attributes to ensure material to be tested in animals and humans is identical to previous lots with consistent stability and bioavailability.	Risk of new impurities due to larger scale operations, the addition of formulation excipients, and processing steps can alter bioavailability in human. Risk that short-term stability tests may not predict long-term results.

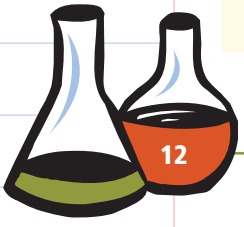


Table II (cont.)

Time	Steps in Discovery, Development and Regulatory Approval	Production Processes, Equipment, Materials, and Personnel	Costs, Risks, Delays and Failures
Three to Five Years (cont.)	**Preclinical, Formulation and Stability Tests (cont.):** Develop clinical trial design and protocol; select sites and assess qualifications, willingness, availability and performance of investigators; prepare investigational new drug (IND) application; package, label, and deliver product to sites.	Develop comprehensive database of physical and chemical properties of API and biopharmacological profile of molecule to evaluate impact of lot-to-lot variation on drug performance due to evolutionary changes in synthesis scale (i.e., the process of turning active compound into a form and strength suitable for human use). Must be able to demonstrate sufficient stability that 90% of the API at a minimum, and only 1% of degradation products at a maximum, are present from time of manufacture until last subject, last dose. Requires preformulation, analytical and formulation scientists.	Chemical and biological studies must also be conducted whenever the dosage form, formulation, or manufacturing process is changed. Formulation development alone can cost $1,000,000.
Four to Six Years	**Clinical Studies:** First set of bioavailability studies are conducted on healthy human volunteers to document rate of absorption and excretion of active ingredients. **Phase I** studies establish tolerance of human subjects to different doses, define its pharmacologic effects at anticipated therapeutic levels and study its absorption, distribution, metabolism and excretion patterns in humans. **Phase II** controlled clinical trials show a compound's potential usefulness and short-term risks. **Phase III** controlled and uncontrolled clinical trials of drug safety and effectiveness for specific indications, identifying range of adverse effects, dose level, and method of use for labeling.	Develop early formulation. Updating rudimentary API to commercial product may require 6-9 months. Equipment for typical clinical trial includes instruments for physical exams & vital signs (e.g., sphygmomanometer), electrocardiogram, clinical lab tests, and miscellanea such as biohazard containers totaling as many as 30 separate items. Disposable materials required for typical clinical trial could include as many as 30 items ranging from syringes to patient slippers. **Phase I:** 20-100 patients and 3 Fiscal Time Equivalents (FTEs). **Phase II:** 100-500 patients and 6-12 FTEs. **Phase III:** 1,000-3,000 patients and 12-20 FTEs. Clinical trials involve data collection and management personnel, research physician and nurse time, tests performed for research purposes, doctor visits, hospital stays, laboratory tests, and X-rays.	Because scope of clinical usage is unknown, have to overproduce investigational product by 25-300%. Equipment costs: $291-318/participant. Disposables costs: $123-129/participant. **Phase I** failure rate: 25%. **Phase II** failure rate: 38.8%. **Phase III** failure rate: 13.2%. Overall, 77% of projects abandoned. Only 11% of patients who respond to clinical trial openings actually enroll; 80% of companies miss enrollment deadlines.

Table continued

Table II (cont.)

Time	Steps in Discovery, Development and Regulatory Approval	Production Processes, Equipment, Materials, and Personnel	Costs, Risks, Delays and Failures
Four to Six Years (cont.)	**Clinical Studies (cont.):** Long-term animal testing must now be done. Conduct pharmacoeconomic studies comparing cost-effectiveness of investigational drug to competing drugs or other health care interventions.	Need bioequivalence studies to prove that investigational product will be equivalent to commercial product, as well as appropriate long-term stability testing (requiring 3-6 months). Develop successor product to early formulation and prototype of commercial product once proof-of-principle is completed, dose must be known from clinical studies and dosing from market studies.	68 trials, 4,235 patients and 50-80 FTEs required per new drug application. Fully loaded FTE costs $125,000/yr. Each day of delay can cost $1.3 million in direct and lost opportunity costs. Costs of pharmacoeconomic studies can be so substantial as to render the overall cost of drug trials infeasible.
One to Two Years	**Approval and Post Approval:** Company must submit new drug application (NDA) to FDA for marketing approval. All information about drug from discovery through development is assembled for NDA and subsequent labeling. After approval, experimental studies and surveillance activities including clinical trials (Phase IV studies) conducted to determine undetectable adverse outcomes (especially in sub-populations), and long-term morbidity and mortality profiles continue.	NDA phase: can involve 20-30 FTEs. Documentation for drug application can require as much as 23 linear feet of storage space and attendant costs for materials, labor, shipping, and storage can be $500,000 to $1 million. Bioavailability studies must be repeated just prior to marketing to ensure that the formulation used to demonstrate safety and efficacy in clinical trials is equivalent to the product that will be distributed for sale. Must design, produce, package and label the product before marketing. Phase IV studies can require thousands of patients and 10-15 FTEs.	During NDA period, FDA may ask for additional information, clarification, or refuse to file or approve application. Other countries have different regulatory processes and requirements, drug may be rejected for reimbursement or other reasons, or require additional studies. 1-in-5 drugs first tested in humans receives approval. Each company pays application, establishment and product fees to FDA every year totaling thousands to millions of dollars. Phase IV study can cost $20-30 million.

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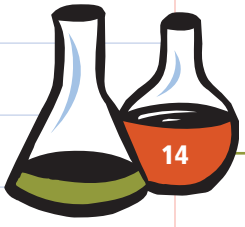

the immune system, and lovastatin and cholesterol biosynthesis.[27] Even drugs that are commercial failures for the drug companies can benefit the public sector because the work done during discovery and development can yield important insight into human physiology and biochemistry.[28]

NIH has long recognized the integral role of the pharmaceutical industry. In its 1997 Director's Panel Report, the NIH stated as one of its 10 recommendations for the effective continuance of clinical research that NIH should ". . . sustain a productive dialogue on enhancing clinical research with its partners: the academic health centers, private foundations, and the pharmaceutical and managed health care industries."[29] The NIH report notes that the $15.1 billion spent by research-based pharmaceutical companies in 1996 "makes the pharmaceutical industry the largest funder in the aggregate of clinical research in the United States."[30] It also points out ". . . that the percentage of NIH's contribution to clinical research as a whole, although considerable. . . may be smaller relative to the other large contributors than was originally thought."[31]

Both the public and private sectors bear the burdens and share the benefits of pharmaceutical R&D. While the burdens and benefits may be different in nature, the risks are incurred in similar terms — time and money. Who should bear these risks? How should limited resources be apportioned among seemingly limitless needs?

Both the public and private sectors bear the burdens and share the benefits of pharmaceutical R&D. While the burdens and benefits may be different in nature, the risks are incurred in similar terms — time and money.

Funding of research, whether by the public or private sector, is an investment decision. The degree of uncertainty, the expected market value, and the potential social benefit are the key factors in determining the appropriate roles for the public and private sectors in health capital investment decisions.[32] Whether such funding is best supplied by the public or private sector involves the interplay of these three key factors. When there is a high level of uncertainty combined with potentially large social benefits in the absence of sufficient patent protection, there is a strong imperative for public investment. Conversely, when the expected market value is high and future use is predictable, private sector funding should suffice. A gray zone exists, however, whenever there is considerable uncertainty. Here a collaboration of public and private funding is appropriate, with sharing of the risks and benefits.[33]

Pharmaceutical companies are hard-pressed to justify research when there is difficulty in obtaining exclusive economic benefits. Patent protection is essential for companies investing in pharmaceutical R&D. Unlike many other technological advances, a drug product, once discovered, is relatively easy to reproduce. Without the period of market exclusivity that patents provide, companies would not have the opportunity to recoup their R&D investments.[34] Yet, patents do not grant complete monopoly power in the pharmaceutical industry because competitors can discover and patent similar drugs that use the same basic mechanism to treat an illness. The first drug using the new mechanism to treat that illness — the pioneer drug — usually has between

one and six years on the market before a therapeutically similar patented drug ("me-too" drug) is introduced.[35] In fact, seven of the 21 impact drugs examined here had a period of pioneer exclusivity of six years or less.[36] Both in the private sector and the public sector, "medical research, like medical practice, is increasingly, and reasonably, challenged to show value for money."[37] Pharmaceutical companies are no exception, and preserving the fruits of decades of labor, through patents and regulatory grants of market exclusivity, is one way firms can show value for money to risk-averse investors.

The public sector also has begun to appreciate the need to protect and profit from its intellectual capital. Over the last two decades, universities have made increasing use of the technology transfer laws passed in the early 1980s, especially the Bayh-Dole Act. Since its enactment, the number of patents issued to universities as well as the number of licenses granted by universities have increased ten-fold, and royalties paid to universities have nearly quadrupled.[38] For its part, NIH recognizes the need to enhance its stewardship of the public's investment in drug discovery and development by enhancing data collection and public access to information on NIH funding of inventive research. However, NIH emphasizes that "requiring direct financial recoupment of the federal investment in biomedical research can potentially impede the development of promising technologies...."[39] Moreover, NIH believes that recoupment strategies "...would destabilize a successful balance between public and private needs for innovation and development."[40]

Summary

Our analysis indicates that the research reported in NIH's case study report and in Cockburn and Henderson's papers has been both misinterpreted and inappropriately used in quantitative analyses of the public and private contributions to drug discovery and development. Both the NIH's and Cockburn and Henderson's methodologies underestimate the contributions of the private sector. The outcome of NIH's analysis of 47 top-selling drugs underscores this fact.

By the same token, our review of the history of 21 impact drugs further illustrates that it is illusory to assign "ownership" of drugs categorically. The biological bases of the diseases alleviated by the 21 impact drugs, as well as the chemical origins of the drugs themselves, were the focus of decades of prior research efforts. The pieces of these research puzzles were pulled together over many decades, by many researchers from many countries, working in both the public and private sectors.

The "reality" of drug discovery is that it relies on a complex chain of interrelated events,[41] and it involves an incremental learning process that takes place over time.[42] The basic research that underlies new therapeutic compounds is a combination of publicly available biomedical knowledge and basic research conducted by firms.[43] There is a high degree of complexity and creativity in the process of drug discovery. Nevertheless, there is a progression in research and learning. To the extent that firms monitor and use publicly available medical knowledge in their research, they can begin the process of drug innovation with something other than a "blank chalkboard."[44]

It is evident that the private sector needs the public sector "to do good science," while the public sector needs the private sector to transform that scientific capital into products that benefit society, and thus to do good medicine.

Enormous changes have occurred within the drug R&D environment since the time period during which the drugs discussed in this paper first began the long road from test tube to pharmacy shelves. The biotechnology industry has flourished as a consequence of the passage of the Bayh-Dole Act and the availability of collaborations and alliances with major pharmaceutical firms. Today, the boundaries between publicly funded and privately sponsored medical research, which were never sharply defined, are even more unclear.[45] Now, as in the past, it is evident that the private sector needs the public sector "to do good science,"[46] while the public sector needs the private sector to transform that scientific capital into products that benefit society, and thus to do good medicine.

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